Q & A Column, 4/14

Editor: Frederick L. Kiechle, MD, PhD

Submit your pathology-related question for reply by appropriate medical consultants. CAP TODAY will make every effort to answer all relevant questions. However, those questions that are not of general interest may not receive a reply. For your question to be considered, you must include your name and address; this information will be omitted if your question is published in CAP TODAY.

Submit a Question

Q. Are the days of DFA in the clinical microbiology lab numbered? How quickly are molecular diagnostic tools replacing DFA? Is this decline a uniform trend or does it depend on the type of clinical microbiology lab?

A. It is clear that advances in technology are changing the practice of medicine, particularly laboratory medicine. Multiplex molecular assays for respiratory viruses have largely replaced direct immunofluorescence antigen (DFA) detection testing and viral culture in many institutions. Although the multiplex molecular assays are particularly useful in hospitalized patients and the immunosuppressed, they should be used judiciously in the outpatient setting to control costs. Probably the best argument for the use of these assays in the outpatient setting is to avoid the unnecessary use of antibiotics by patients with viral infections. If the test is performed for this reason, then it is important that results be used accordingly. If all patients with viral infections are going to leave "covered" with antibiotics, then the test—although comforting because a diagnosis was achieved—did not have the full therapeutic impact, nor did it help control the spread of antimicrobial resistance.

There are, however, other instances wherein the positive and negative predictive values of DFA tests approach that of PCR, and the slight differences in sensitivity when weighed against turnaround time and cost do not have a clinical impact. For example, in a recent evaluation, even though two PCR assays were slightly more sensitive than DFA for the detection of varicella-zoster virus (VZV) from skin lesions, the sensitivity, specificity, and positive/negative predictive value of DFA was shown to also be very good and remains our mainstay of diagnosis for this virus in these specimens. The detection of VZV from CSF would be a different challenge, wherein PCR would be expected to greatly outperform both DFA and culture.

Therefore, the clinical impact and the cost-benefit ratio should be considered whenever two tests are compared. In some instances, the new diagnostic tests will prove superior, whereas in other instances the traditional test will remain the most useful diagnostic tool. For example, no molecular test has a sensitivity that exceeds that of culture for the detection of *M. tuberculosis*, but in order to determine if an AFB-smear positive specimen contains *M. tuberculosis* versus a nontuberculous mycobacteria, molecular diagnostics clearly add value. The patient population served and an assessment of the clinical impact of slight differences in sensitivity of the diagnostic tests being considered should inform test selection, with cost a secondary but important parameter.

1. Wilson DA, Yen-Lieberman B, Schindler S, Asamoto K, Schold JD, Procop GW. Should varicella-zoster virus culture be eliminated? A comparison of

direct immunofluorescence antigen detection, culture, and PCR, with a historical review. *J Clin Microbiol.* 2012;50(12):4120–4122.

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Q. I have a question about the meaning of the word "guideline" versus "procedure." Checklist requirement ANP. 11670 Specimen—Gross Examination says the following: "Documented instructions or guidelines are readily available in the laboratory for the proper dissection, description, and histologic sampling of various specimen types (e.g. mastectomy, colectomy, hysterectomy, renal biopsy, etc.)." This leads me to question whether the word guideline means the same as procedure. Procedures need to be signed biennially. Does the same apply to guidelines? The formatting is different for procedures. Could guidelines also mean references?

A. While the availability of published reference texts or manuals can be interpreted as fulfilling the minimal requirements for compliance with ANP. 11670, it is still strongly encouraged that further laboratory-specific procedures be outlined in a departmental grossing manual. This is analogous to not allowing package inserts in the clinical areas in lieu of laboratory-specific procedures. Each facility can determine the comprehensiveness of the grossing and reporting manual, but it is important that there be in this manual at least some departmentally developed guidelines to specimen grossing. These should incorporate facility-specific issues for certain specimen types that may exist within your group or institution. There may also need to be specific elements appropriate for the patient population served and relative volume of various specimen types received.

Most labs have available the grossing procedures found in the back of the Ackerman/Rosai textbook; there is no need to reinvent the wheel and write an on-site grossing manual when excellent references already exist. However, every laboratory has unique situations that should be specified—for example, what specimens are handled as gross only and which ones require microscopy—decisions made in conjunction with clinical departments such as surgery and orthopedics. These will always differ from hospital to hospital based on clinical case mix. Nerve/muscle biopsies that are usually sent out are another example. Use of clamps, for instance, and how the specimens are packaged for shipment should be part of the standard operating procedure.

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Q. On urine cytologies (voided collections) are there numbers on how often the findings of suspicious for malignancy for groups of atypical cells for a neoplasm believed to be urothelial are found to be from another source, even a metastasis, such as breast cancer? Can you provide the citations? Are there new or better processes or procedures to avoid discrepancies? Who is working on this?

A. There are few large studies in the literature dealing specifically with urine cytology detection of nonurothelial tumors. Most citations are case reports or small series. Investigators at Memorial Sloan-Kettering Cancer Center retrospectively evaluated 55,946 urine cytology specimens from 12,705 patients over a 12-year period and correlated cases with biopsy findings.[1] One hundred eight patients had adenocarcinoma, and of these 86 percent originated from the urinary tract. Forty-seven percent of 110 patients with squamous cell carcinoma had primary

urinary tract disease.

What nonurothelial tumors might be expected to appear in urine cytology? Bates and Baithun evaluated 282 secondary bladder neoplasms and discovered that 21 percent originated from the colon, 19 percent from the prostate, 12 percent from the rectum, and 11 percent from the cervix.[2] Most of the tumors involved the bladder through direct extension from the primary site. For metastatic sites, stomach was most common (4.3 percent), followed by skin (3.9 percent), lung (2.8 percent), and breast (2.5 percent). The majority of these tumors present as solitary metastatic deposits in the bladder neck or trigone.

In one large study from Loyola University Medical Center examining 1,320 atypical urine cytologies from 16,299 urine specimens over an 11-year period, 21 percent progressed to a positive cytologic or surgical biopsy, and all of the specimens were of urothelial origin.[3] The authors of the study concluded that upper urinary tract specimens had the highest correlation with urothelial malignancy in this group. McCroskey, et al., reported a case of myeloid leukemia detected in urine cytology.[4] In a study of 21,557 voided urines from Bangalore, India, 1,424 had gross hematuria, and of these 464 (32.5 percent) had atypical cytology and 136 (9.5 percent) had a malignant biopsy—all of them urothelial in origin.[5] Massachusetts General Hospital reported on atypical urine cytology in 201 consecutive voided urines in a tertiary care setting, and all of the biopsy-confirmed malignancies were urothelial carcinoma (23.4 percent, or 47 cases).[6]

In summary, the detection of nonurothelial neoplasms of the bladder in urine cytology is uncommon, and most of these tumors originate from the bladder. These tumors may be interpreted initially as atypical urothelial cells. Urine cytology can also be used to diagnose these lesions, and ancillary studies can assist in determining the cell or site of origin.

1. Raj GV, Bochner BH, Vickers A, et al. Association between urinary cytology and pathology for nontransitional cell malignancies of the urinary tract. *J Urol.* 2006;175(6):2038–2041.
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3. Muus Ubago J, Mehta V, Wojcik EM, Barkan GA. Evaluation of atypical urine cytology progression to malignancy. *Cancer Cytopathol.* 2013;121(7):387–391.
4. McCroskey Z, Mehta V, Wojcik EM, Barkan GA. Myeloid leukemia in a urine specimen: a case report and review of the literature [published online ahead of print June 8, 2013]. *Diagn Cytopathol.* doi:10.1002/dc.23017.
5. Siddappa S, Mythri K, Kowsalya R. Cytological findings in routine voided urine samples with hematuria from a tertiary care center in south India. *J Cytol.* 2012;29(1):16–19.
6. Deshpande V, McKee GT. Analysis of atypical urine cytology in a tertiary care center. *Cancer.* 2005;105(6):468–475.

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